

Bregenz); J W Dudenhausen (Freie University of Berlin); E Fleck (German Heart Centre); I Guggenmoos-Holzmann (chair); U Gundert-Remy (University of Gottingen); K Kunze (Uniklinik Hamburg-Eppendorf); N Victor (University of Heidelberg); C Zippel (Klinik für innere Medizin und Rehabilitation, Berlin).

#### TRANSNATIONAL CASE-CONTROL STUDY GROUP

*Potsdam coordinating centre*—V Anning, A Assmann, C Kluhworth, D Kuhl-Habich, M Lewis (head of international data management), J Von Rosen.

*Senior investigators*—J P Boissel (Hôpital Neuro-Cardiologique, Lyons); R Bruppacher (University of Basle); L Heinemann (Zentrum für Epidemiologie und Gesundheitsforschung); M Lewis; K MacRae (principal medical statistician); N Poulter (University College London Medical School); W O Spitzer (principal investigator) (McGill University); M Thorogood (London School of Hygiene and Tropical Medicine).

*Centres*—Austria: R Brugger, H Concin (director), S K Fuchs, I Michalek, C Trotter (Bregenz); S Hascher, S Loibner, G Stark (director) (Graz); S Alge, S Hammerle, H Jud, B Kittinger, C Pechlaner, K Pfeiffer (director), H Ulmer (Innsbruck); B Gappmeyer, S Humpeler, Weitgasser (director), G Scheurer (Salzburg). France: H Barlet, M Baumevielle, B Begaud (director), A Chaslerie, F Haramburu, F Penouil (Bordeaux); B Boissel (director), C Cornu, J Gillet, A Le Goff, B Ravis, N Strang (Lyons (national coordinating centre)). Germany: W Barth, H Behr, L Heinemann (director), T Leonhard, B Lorenz, F Masius, K-H Mauritz, S Moehner, B Sykura, C Thiel, O J Titlbach, C Toussaint (Berlin (national coordinating centre)); J Busse, W Fleig, J Haerting (director until July 1994), M Hagert, H Klette, F Lautenschlaeger (director since July 1994), H Liebal, H Podhasky, W Teichmann, S Zierz (Halle); A Heinemann, U Lockemann, K Pueschel (director) (Hamburg); F Hoffmann (director), G Grohmann, U Merkel (Jena); B Bremer, D Haase, W Hellenbrand, C Kalninsch, C Listing, B-P Robra (director), M Schwarz (Magdeburg); M Lustermann (director) (Nordhausen); I Schulzki

(director), H Voigt (Schwerin); S Boethig (director), C Lorenz (Zwickau). Switzerland: B Candinas, F Gutzwiller (director), U Kaser, N Pua, J Schilling (Zurich). United Kingdom: L de Caestecker (director), E Hamilton, S Mitchell, M Soler-Lopez (Glasgow); D Curle, J Gibbs, H Hemingway, G Mein, M Thorogood, N Poulter, S Smith (London (national coordinating centre)); P Hannaford (director since August 1995), Z Evans, B Faragher, S Ferry, G McHugh, C McCollum (director until August 1995), C Sutcliffe (Manchester); A Ascott, N Dunn, R Mann (director), B Weston (Southampton).

*Consultants*—D Liberthson for technical writing, Y Lis (Carter-Lis Associates), M W L Davis (McGill University) for quality assurance; M Sands (Stanford University) for bibliography.

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## Third generation oral contraceptives and risk of myocardial infarction: an international case-control study

Michael A Lewis, Walter O Spitzer, Lothar A J Heinemann, Kenneth D MacRae, Rudolf Bruppacher, Margaret Thorogood on behalf of Transnational Research Group on Oral Contraceptives and the Health of Young Women

### Abstract

**Objective**—To test whether use of combined oral contraceptives containing third generation progestogens is associated with altered risk of myocardial infarction.

**Design**—Matched case-control study.

**Setting**—16 centres in Austria, France, Germany, Switzerland, and the United Kingdom.

**Subjects**—Cases were 153 women aged 16-44 with a myocardial infarction event. Controls were 498 women (at least 3 controls per case) unaffected by myocardial infarction who were matched with their corresponding case for age and for hospital or community setting within four months of the index infarction.

**Main outcome measures**—Odds ratios derived with stratified analyses and unconditional logistic regression to adjust for potential confounding variables.

**Results**—The estimated odds ratio for myocardial infarction of third compared with second generation oral contraceptives among all 651 study subjects was 0.36 (95% confidence interval 0.1 to 1.2) ( $P=0.11$ ). The odds ratio for the United Kingdom and Germany alone was 0.45 (0.1 to 1.8) ( $P=0.26$ ). Other odds ratios for the five countries were 3.1 (1.5

to 6.3) ( $P=0.003$ ) for use of second generation products *v* no current use and 1.1 (0.4 to 3.4) ( $P=0.9$ ) for use of third generation products *v* no current use. Among the confounding variables the independent contribution of smoking (for which adjustment was made in the above estimates) proved to be important (10.1 (5.7 to 17.9),  $P<0.001$ ).

**Conclusion**—An odds ratio of 0.45 with wide confidence intervals shows that third generation oral contraceptives compared with second generation products are associated with a reduced risk of myocardial infarction or with no difference. This finding from an interim analysis should be interpreted with extreme caution. However, the excess risk of venous thromboembolism associated with the use of third generation products may be balanced by the reduced risk of myocardial infarction associated with the same products.

### Introduction

The aim of the transnational project was to examine the safety of the third generation combined oral contraceptives, which contain the progestogens gestodene and desogestrel. At the outset gestodene was of special interest because of concerns in the European

See p 83 and editorial by McPherson

The full list of members of the group is given at the end of the accompanying article (p 83)

Correspondence to: Professor W O Spitzer, Potsdam Institute of Pharmacoepidemiology and Technology Assessment (PIPTA), Otto Erich Strasse 7, 14482 Potsdam, Germany.

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**Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada**

Michael A Lewis,  
assistant professor  
Walter O Spitzer,  
Strathcona professor of preventive medicine

**Centre for Epidemiology and Health Research, Zepernick/Berlin, Germany**

Lothar A J Heinemann,  
director

**Charing Cross and Westminster Medical School, London**

Kenneth D MacRae,  
reader in medical statistics

**Potsdam Institute of Pharmacoepidemiology and Technology Assessment (PIPTA), Potsdam, Germany**

Rudolph Bruppacher,  
senior epidemiologist

**London School of Hygiene and Tropical Medicine, London**

Margaret Thorogood,  
senior lecturer

regulatory agencies and prominent discussion in the medical and lay press. The project incorporated three matched case-control studies with virtually identical methods<sup>1,2</sup> for which the exposure factor of particular interest was use of third generation oral contraceptives. The outcomes for the three studies were venous thromboembolism, myocardial infarction, and ischaemic (thrombotic) stroke. Results of the study testing an association between the third generation products and venous thromboembolism are reported in the accompanying article.<sup>3</sup> We report here the initial results of the case-control study assessing and contrasting the relation between second and third generation oral contraceptives and myocardial infarction in young women. Case recruitment continues. Identification and quantification of publicity bias will be incorporated in an amended protocol if extended field work proves feasible in the United Kingdom.

### Subjects and methods

The subjects were women aged 16-45 who were recruited in 16 centres in five countries (Austria, France, Germany, Switzerland, and the United Kingdom). In this paper we include results for all five countries as well as for the United Kingdom and Germany alone to permit concurrent evaluation of our results on venous thromboembolism and myocardial infarction. An average of three controls was matched to each case; at least one control was from a hospital and at least one from the community. We matched for age in five year age bands. The cases of myocardial infarction (*International Classification of Diseases* code 410) met the criteria of the World Health Organisation.<sup>4</sup> Controls were identified and interviewed within four months of the myocardial infarction of the index case. Current use of oral contraceptives was defined as use within three months before the event for a case, the date of admission for a hospital control, and the date of interview for a community control. The field work, beginning with feasibility and pilot projects, started in July 1991, and case recruitment continued until November 1995. Recruitment of controls for this report continued until 15 November 1995.

We assessed current use of third generation oral contraceptives containing low doses of ethinyl oestradiol (usually 30 µg or 20 µg) and one of two progestogens, gestodene or desogestrel. Second generation oral contraceptives (the main reference group) are other low dose ethinyl oestradiol prepara-

tions (under 50 µg) with progestogens introduced to the market earlier. We report unmatched odds ratios with 95% confidence intervals and their P values. We combined community controls and hospital controls as our main reference group. Odds ratios were calculated by unconditional logistic regression to adjust for the potential confounders listed in the footnote to the table, of which current smoking was deemed to be the most important. We estimated the effect of smoking adjusted for use of oral contraceptives. Matched analyses were done as a sensitivity check and to determine whether overmatching may have occurred. Further details on methods have been published<sup>1,2</sup> or are available from us. We used a general plan and operational procedures virtually identical with those of the WHO's study group<sup>4</sup> on oral contraceptives to facilitate comparison of the results of that project with those of the transnational project.

We have outlined the method we used to calculate the number of lives "saved" by switching from second to third generation oral contraceptives in the accompanying paper.<sup>3</sup>

### Results

We enrolled 153 cases of myocardial infarction (11 of them fatal) and 498 controls. Eighty two cases were identified in the United Kingdom, 47 in Germany, five in Switzerland, six in Austria, and 13 in France. When we compared current use of third generation with current use of second generation products as risk factors for myocardial infarction in all 651 women the odds ratio was 0.36 (0.1 to 1.2) (P=0.1; table 1). When current use of third generation products was compared with no previous use of oral contraceptives the odds ratio was 0.3 (0.1 to 1.0) (P=0.06). When we excluded the three countries with small sample sizes (Austria, Switzerland, and France) the estimates and confidence intervals became 0.45 (0.1 to 1.8) (P=0.26) for use of third generation v second generation products; 1.0 (0.3 to 3.5) (P=0.96) for current use of third generation products v no current use of oral contraception; and 2.2 (1.0 to 5.0) (P=0.07) for current use of second generation products v no current use.

When we compared women who currently used third generation oral contraceptives with those who currently used second generation products we considered the controls as two groups matched for hospital or community. The odds ratio was 0.91 (0.2 to 4.7) (P=0.9) for cases and hospital controls and 0.25 (0.06 to 1.0) (P=0.05) for cases and community controls.

In matched analyses the odds ratio was 0.40 (0.1 to 1.6) (P=0.19) in the comparison of third v second generation oral contraceptives. The odds ratio for second generation products v no use, was 3.1 (1.4 to 6.8) (P=0.01) and for third generation products v no current use 1.2 (0.34 to 4.4) (P=0.76). When current smoking was adjusted for use of oral contraceptives the odds ratio for the risk of myocardial infarction was 10.1 (5.7 to 17.9) (P<0.001) among our study subjects. Among women who used third generation products the crude odds ratio for current smoking was 3.1 (0.5 to 19.8) (P=0.23). Among those who used second generation products it was 11.1 (3.0 to 40.2) (P<0.001), and for women who were not current users of oral contraceptives the equivalent risk estimate was 7.7 (4.0 to 14.7) (P<0.001).

Given the prevalence of use of third and second generation preparations in the controls of this study, the observed odds ratio of 0.36 (0.1 to 1.2) for third compared with second generation products is consistent with a switch from second to third generation oral contraceptives, resulting in 12 fewer deaths from acute myocardial infarction per year in England and Wales. The confidence interval for the number of

**Table 1—Odds ratios\* for risk of myocardial infarction for current use of different types of oral contraceptives: principal results of transnational study**

Comparison	Odds ratio (95% confidence interval)	P value	No exposed cases; No exposed controls
<b>All cases (n=153)</b>			
<b>All controls (n=498)</b>			
Third generation v second generation products	0.36 (0.1 to 1.2)	0.1	6; 34
Third generation products v no current use	1.1 (0.4 to 3.4)	0.9	6; 34
Second generation products v no current use	3.1 (1.5 to 6.3)	0.003	23; 45
<b>Hospital controls (n=210)</b>			
Third generation v second generation products	0.91 (0.2 to 4.6)	0.9	6; 11
Third generation products v no current use	1.9 (0.4 to 8.7)	0.4	6; 11
Second generation products v no current use	2.0 (0.8 to 4.9)	0.1	23; 26
<b>Community controls (n=288)</b>			
Third generation v second generation products	0.25 (0.1 to 1.0)	0.05	6; 23
Third generation products v no current use	0.9 (0.3 to 3.0)	0.8	6; 23
Second generation products v no current use	3.5 (1.5 to 8.6)	0.005	23; 19

\*Adjusted for centre, age, body mass index, smoking, alcohol intake, and duration of exposure to oral contraceptives before current contraceptive.

deaths gives a range from 18 fewer to three more deaths from acute myocardial infarction per year in England and Wales. In Germany the range is from 65 fewer deaths to 14 more; the point estimate is consistent with 46 fewer deaths annually with a switch from second to third generation oral contraceptives.

### Discussion

Odds ratios for the risk of myocardial infarction ranged from 0.30 to 0.45 when we compared third generation with second generation oral contraceptives. These results are based on only six cases of acute myocardial infarction and 34 controls exposed to third generation oral contraceptives and on 23 cases and 45 controls exposed to second generation products. This is reflected in the crude odds ratio for the individual study components, which ranged from 0.06 (0.01 to 0.76); for one case and six controls) in the southern region (Austria, France, Switzerland) to 1.07 (0.25 to 4.55); for four cases and 18 controls) in the United Kingdom, with Germany having intermediate values (0.18 (0.02 to 1.62); for one case and 10 controls). The combined odds ratio for continental Europe was 0.15 (0.03 to 0.72); for two cases and 16 controls). The overall, fully adjusted odds ratio for all five countries was 0.36 (0.1 to 1.2). The point estimates are consistent with a benefit in the range of twofold to fourfold for those who use third generation rather than second generation oral contraceptives. This finding is from an interim analysis so should be interpreted with caution. If the findings are confirmed by subsequent work, it would translate into an important public health message. The excess risk of venous thromboembolism associated with the use of third generation oral contraceptives may be offset by the reduced risk of acute myocardial infarction when compared with second generation products.

As for the accompanying study, this study may be biased in terms of diagnosis, exposure selection, as well as attrition of susceptible subjects (a potential bias described in the accompanying article).<sup>3</sup> Adjustment for duration of use of current oral contraceptives reduced the odds ratios further for the comparisons between third and second generation products. Matched analyses suggest strongly that overmatching did not occur. We showed that cigarette smoking was associated with a much higher risk of heart attack than the use of either generation of oral contraceptives.

These results are from only one study. Experimental, clinical, and laboratory studies both support and contradict the epidemiological findings.<sup>8,9</sup> They cannot and should not be invoked to indict second generation oral contraceptives. The benefits of the well established low dose second generation oral contraceptives clearly outweigh their risk, particularly in developed and developing countries where third generation preparations have not been approved or are not available. They have dropped to half or less of the odds ratios observed in the epidemiological studies of oral contraceptives in the mid-1970s.<sup>10,11</sup> The accompanying paper shows that products containing levonorgestrel, in particular, had low profiles of risk.<sup>3</sup> The risks associated with pregnancy still heavily outweigh those associated with the use of any oral contraceptive. Women incur many risks, including smoking, with higher likelihood of harm than the probabilities of myocardial infarction associated with the use of oral contraceptives reported here.

Our findings on the potential benefits of third generation oral contraceptives with respect to the risk of myocardial infarction against the backdrop of

### Key messages

- This European case-control study addressed recently raised concerns about the role of third generation oral contraceptives in the occurrence of myocardial infarction
- Compared with the results of British studies published in the 1970s, the risk of myocardial infarction among current users *v* non-users of second generation oral contraceptives was low
- The risk of myocardial infarction was appreciably lower among women using third generation products, the risk being comparable to that among women who did not use oral contraception and two to three times lower than that among women using second generation products
- The results suggest that about 12 fewer deaths from myocardial infarction in England and Wales and 46 fewer in Germany would occur each year if all those taking second generation oral contraceptives started taking third generation products
- Both the risks and the benefits of oral contraceptives need to be considered in a balanced way so that doctors can give judicious advice and women have informed choice

potential harm with respect to risk of venous thromboembolism show that all known risks and benefits should be evaluated simultaneously when decisions about such products are taken. Both generations of oral contraceptives can be recommended on the basis of judicious clinical advice by the doctor and the informed choice of the woman using contraception.

The investigators were accountable only to the scientific reference board (members listed at the end of the accompanying paper<sup>3</sup>), which approved the protocol, received periodic reports, and conducted audits on the field and of the data before submission. The board was also advised on statistical issues by the statistical advisory group (members listed in the accompanying paper<sup>3</sup>).

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